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Comparison of the Family History With the Family Study Method: Report From the Camberwell Collaborative Psychosis Study

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We assessed the accuracy of the family history (FH-RDC) and family study (SADS-L) methods for obtaining information about the presence of psychopathology in 274 first-degree relatives of patients with psychotic disorders. The family history method had only modest sensitivity, 40.8% for affective disorders and 58.6% for psychotic disorders, but high specificity, 94.1% for affective disorders and 98.7% for psychotic disorders. For both disorders, sensitivity was higher for relatives who had had previous psychiatric admissions. However, with the family study method, we found that relatives with affective disorder were more likely to be interviewed than those relatives with other disorders. Hence, the family study method may be prone to selection bias that distorts morbid risk estimates. We conclude that the best way of collecting information regarding family psychopathology is to interview directly as many relatives as possible and to collect supplementary family history information on unavailable relatives. ***Am. J. Med. Genet. 74:12–17, 1997.*** **© 1997 Wiley-Liss, Inc.**

KEY WORDS: family history; family study; relatives; sensitivity; specificity

INTRODUCTION

There are many questions concerning the nature of the genetic contribution to the aetiology of psychiatric disorders. To answer these, it is vital to have methods for obtaining accurate information about psychopathology in relatives. Two techniques are generally used for gathering this information: the family history method and the family study method. Each has its advantages and limitations.

The family history method involves obtaining information from the proband or a relative about all other family members. In contrast, the family study method involves the direct interview of each family member concerning his or her own symptoms. The main advantages of the family history method are that it less time consuming than the family study method and that information can be collected on family members not available for direct interview because of refusal to participate, emigration, or death. The major disadvantage of the family history method is its low sensitivity. Some studies have shown that ⅓–⅔ of relatives suffering from affective disorders are missed by this method [Mendlewicz et al., 1975; Andreason et al., 1977, 1986; Thompson, 1982; Gershon and Guroff, 1984; Zimmerman et al., 1988]. Although less prone to information bias, the family study method may suffer selection bias if there are systematic differences between those relatives who are available for interview and those who are not.

Investigators have attempted to identify factors that may improve sensitivity and guide informant selection. Results about the optimal relationship of the informant with the relative are conflicting. Andreason [1986] reported that parents were better informants than either siblings or offspring, whereas Thompson et al. [1982] found that spouses and offspring were more accurate than parents. Informants identified as suffering from depression were reported to be more sensitive to illness in their relatives [Chapman et al., 1994]; similarly, the affected twins in those pairs discordant for depression or anxiety were found to be more accurate in identifying relatives with the same disorder than their well cotwins [Kendler et al., 1991]. As expected, increasing the amount of information available by the use of multiple informants improves sensitivity [Gershon and Guroff, 1984], but the effect is small [Thompson et al., 1982; Mendlewicz et al., 1984]. Findings concerning the characteristics of those affected relatives who are identified as ill by an informant are more consistent. Female sex, severe illness, and hospitalisation are associated with positive reporting of depression by informants [Orvaschel et al., 1982].

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Most studies comparing the family history and family study methods have focused on the relatives of probands with affective disorder. In this study we compare the two methods as applied to a study of functional psychotic disorders. Our specific aims were: (1) to assess the sensitivity and specificity of the family history method in identifying both psychotic and affective disorders in the first-degree relatives of probands with a psychotic disorder, (2) to account for discrepancies between the two methods by identifying proband, informant, and relative characteristics that are predictive of disagreement, and (3) to investigate sources of selection bias that may influence the reported rates of psychiatric illnesses among relatives in studies that use the family study method.

MATERIALS AND METHODS

Subjects and Assessments

A survey was taken of admissions for psychosis to three south London psychiatric teaching hospitals from March 1987 to February 1988 and from October 1988 to August 1989. A total of 195 patients were included, aged 16–50 years, who were admitted with delusions, hallucinations, or thought disorder in clear consciousness. Those admitted to the alcohol, adolescent, mental handicap, and regional secure units, and those for whom alcohol was a major aetiological factor were excluded. In the first study period, subjects were included only if their mothers were alive and living in the UK or Eire, so that family history could be obtained by interview. In the second period, the availability of the mother was not an inclusion criterion for first onset cases; however, all but nine interviews were conducted with the mother as informant.

Probands were interviewed with the Present State Examination (PSE, 9th edition) [Wing et al., 1974]. This information together with that from case notes was used to derive RDC and DSMIII diagnoses, blind to information regarding the relatives' interviews. Information regarding first-degree relatives was obtained from three sources: interview with the proband's mother (or another first-degree relative in nine cases), medical records of relatives who had ever been admitted to a psychiatric hospital, and the probands' case notes. Mothers were interviewed with FH-RDC [Andreason et al., 1986]. All information from the above sources concerning the relatives was then independently rated by two researchers, who were blind to any data regarding the proband. A high degree of interrater reliability, as assessed by kappa coefficients, was achieved [Sham et al., 1993] and a consensus diagnosis was reached in cases of disagreement. The final diagnosis reached by this method used a combination of sources of information, obviously excluding that obtained by direct interview. The diagnosis reached is considered throughout this report as the "best FH estimate" diagnosis.

Direct interview assessments of individual relatives using the Schizophrenia and Affective Disorder Schedule—Lifetime version (SADS-L) [Endicott et al., 1978] were performed during the period from 1989 to 1993. Attempts were made to contact all 887 first-degree relatives who were identified (194 mothers, 194 fathers, and 499 siblings). Unfortunately, it was not possible to contact all mothers who had participated in the FH-RDC interviews. Relatives who agreed to participate were interviewed by raters who were blind to all previously collected information.

Statistical Analyses

In order to assess the representativeness of the relatives who were directly interviewed with SADS-L, we compared these relatives with those for whom we had information only according to the family history method. The data were tabulated and Chi-square tests of homogeneity of proportions performed. Next, we assessed the level of agreement between the best FH estimate and SADS-L diagnoses, among individuals who were assessed by both methods. As well as tabulating diagnoses made by the family history method against SADS diagnoses, we calculated the sensitivity and specificity of best FH estimate diagnoses, regarding the SADS diagnosis as the reference diagnosis. These indices were defined as:

sensitivity = number of affected individuals identified by the family history method/number of affected individuals by the family study method.

specificity = number of unaffected individuals identified by the family history method/number of unaffected individuals by the family study method.

Finally, we attempted to clarify the factors that influence the relationship between the best FH estimate and SADS-L diagnoses. We hypothesised that best FH estimate diagnoses were influenced by the age, ethnicity, and psychiatric status of the informant (usually the mother), the severity of illness in the relative, as well as the SADS-L diagnosis or reference diagnosis. The effects of these influences were examined simultaneously using logistic regression analysis as implemented in SPSS-PC. Two separate analyses were performed, one examining the predictors of a best FH estimate diagnosis of major depression and the other examining the predictors of a psychotic best FH estimate diagnosis. In both analyses, the predictor variables entered were the SADS-L diagnosis of the relative, the age, sex, ethnicity of the relative, the number of hospital admissions experienced by the relative, whether the relative was the mother of the proband (i.e., whether the relative was also likely to be the informant), and the diagnosis of the informant. Possible interactions between SADS-L diagnosis of the relative and each of the other predictors variables were also examined in the logistic regression analysis. The forward stepwise procedure using the likelihood ratio option was used because of the large number of predictors variables examined.

RESULTS

A total of 925 first-degree relatives were identified, with information from informants available for 891, of whom 274 (31%) were interviewed.

Representativeness of SADS-L Sample

Relatives who were interviewed directly with the SADS-L were compared with those who were not. Females were more likely to have a SADS-L interview than males (59.8% of the SADS-L sample were female vs. 48.5% in the total sample). SADS-L interviews were completed with 53.6% of mothers compared with only 32.5% of fathers and 21.4% of siblings ($P < 0.0001$). Of the siblings, 22.5% of brothers were interviewed and 34.5% of sisters. Interviews were more frequently completed in older relatives. The mean age of those interviewed was 45.8 years (SD 15.7) compared with 37.2 years (SD 17.1) for those who were not interviewed. However, there was no significant difference between the mean age of the siblings or parents who were interviewed and those who were not. The difference in age distribution between the two groups can therefore be explained by the relative proportions of parents and siblings in the groups. There was a significant difference between the ethnic composition of the interviewed and noninterviewed groups with 39% of white British relatives being interviewed compared with 18.7% of nonwhite British relatives ($P < 0.0001$).

Diagnostic categories were available for the whole sample from the family study-derived best estimates. Only 35.5% of relatives with no psychiatric diagnosis agreed to be interviewed compared with 61.8% of those with a diagnosis of major depression, 62.5% with bipolar affective disorder, 62.5% with schizoaffective disorder, 50% with unspecified functional psychosis, and 33.3% with schizophrenia (Table I).

Comparison of Best FH Estimate With SADS-L Diagnoses

The overall level of agreement between the diagnoses derived from the family study method and the SADS-L interview is presented in Table II. For major depression, the sensitivity of best estimate diagnoses was 40.8% (95% C.I. 26.8–54.8), whereas the specificity was 93.2% (95% C.I. 89.7–96.7) As the numbers in the psychotic diagnostic categories were small and identification of psychotic symptoms seemed the most important common feature required to generate a best FH estimate diagnosis of bipolar affective disorder, unspecified functional psychosis, schizoaffective disorder, or schizophrenia, these diagnostic categories were combined into one "psychotic" group. The sensitivity and specificity for "psychosis" as a whole was then calculated. In our sample, the sensitivity was found to be 60% (95% C.I. 42.1–77.9), whereas the specificity was found to be 98.7% (95% C.I. 97.2–100).

Predictors of Best FH Estimate Diagnoses

Forward stepwise logistic regression showed that the factors that significantly predicted a best FH estimate diagnosis of major depression were: (1) SADS-L diagnosis of major depression in the relative ($P < .0001$), (2) number of hospital admissions ($P < .0001$), and (3) age of the relative ($P = .004$). These effects are illustrated by comparing sensitivities for the best estimate diagnoses after separating groups by these significant factors, as shown in Tables III and IV.

The significant predictive factors for best FH estimate diagnosis of psychosis were: (1) a SADS-L diagnosis of psychosis in the relative ($P = .0001$), (2) number of hospital admissions ($P = .007$), (3) a SADS-L diagnosis of depression in the relative ($P = .04$), and (4) an interaction between a SADS-L diagnosis of psychosis and ethnicity ($P = .03$). These effects were illustrated by comparing sensitivities between groups selected by number of admissions and ethnicity (see Tables III and V).

Unlike previous studies, we did not find that the presence of symptoms in the informants predicted rates of reporting of psychopathology for their relatives, although the wide confidence limits suggest that our sample may have been too small to demonstrate such an effect. Sensitivity for diagnosing depression by mothers with no psychopathology was 45% (95% C.I. 23–67) and specificity 96% (95% C.I. 88–100), whereas mothers with depression had a sensitivity of 50% (95% C.I. 10–90) and specificity of 96% (95% C.I. 88–100). The number of psychotic mothers was too small to demonstrate an effect upon their accuracy of reporting.

DISCUSSION

We found a highly significant difference in the prevalence of psychopathology, ethnicity, and relationship to proband between the two samples. Unlike previous studies [Andreason et al., 1977, 1986] that compared the family study method with the family history method, we found systematic sampling bias on comparing those relatives who were available for interview with those who were not interviewed.

A greater proportion of relatives with affective disorder were interviewed, whereas fewer than half of those with no psychopathology or with psychotic disorders were interviewed. These findings would obviously lead to an overestimate of the morbid risk for affective dis-

TABLE I. Diagnoses of Interviewed Relatives*

	NP[a]	MD[b]	BPA[c]	UFP[d]	SZA[e]	SZ[f]	Total
Interviewed with SADS-L	200 (35.1)	34 (61.8)	5 (62.5)	4 (50)	5 (62.5)	7 (33.3)	255
Not interviewed	370 (64.9)	21 (38.2)	3 (37.5)	4 (50)	3 (37.5)	14 (66.6)	415
Total (row %)	570 (85.1)	55 (8.2)	8 (1.2)	8 (1.2)	8 (1.2)	21 (3.1)	670

[a] No psychopathology.
[b] Major depression.
[c] Bipolar affective disorder.
[d] Unspecified functional psychosis.
[e] Schizoaffective disorder.
[f] Schizophrenia.
* $P < 0.001$.

TABLE II. Comparison of SADS-L and Best FH Estimate Diagnoses

Best FH estimate diagnosis	SADS-L diagnosis						
	NP[a]	MD[b]	UFP[c]	BPA[d]	SZA[e]	SCZ[f]	Total
NP[a]	164	27	0	6	1	2	200
MD[b]	11	20	0	2	1	0	34
UFP[c]	0	2	1	1	0	0	4
BPA[d]	0	0	0	3	2	0	5
SZA[e]	0	0	0	0	5	0	5
SCZ[f]	1	0	0	0	0	6	7
Total	176	49	1	12	9	8	255

[a] No psychopathology.
[b] Major depression.
[c] Unspecified functional psychosis.
[d] Bipolar affective disorder.
[e] Schizoaffective disorder.
[f] Schizophrenia.

TABLE III. Determinants of Best FH Estimate Diagnoses—Hospital Admissions

SADS diagnosis	No psychopathology			Major depression			Psychosis		
Number of admissions	0	1	>1	0	1	>1	0	1	>1
Cell count	172	2	1	37	5	6	9	2	19
Best FH estimate (BE) diagnosis of depression	10	0	1	13	3	4	0	0	3
Sensitivity of BE diagnosis of depression (%)	—	—	—	35	60	67	—	—	—
Best FH estimate (BE) diagnosis of psychosis	0	0	0	0	1	1	1	1	16
Sensitivity of BE diagnosis of psychosis (%)	—	—	—	—	—	—	11	50	84

order and an underestimate of the risk of psychotic disorders in the relatives of psychotic probands if individuals who did not participate in the family study were excluded from the analysis. This finding must be interpreted with caution as the rates of psychopathology were assessed using informant data that we have shown has only moderate sensitivity. It seems likely that those individuals who refused to participate were more reluctant to report their psychiatric symptoms to the informant than those who were interviewed. It is therefore possible that the apparent group difference reflects higher rates of false negative findings among individuals who refused interviews.

Two factors suggest that we may have found a real difference between the two groups. First, as our interviewed sample was older than the noninterviewed sample, a greater proportion will have passed the period of highest risk for affective disorder. Second, a greater proportion of the directly interviewed relatives were parents who may have been symptomatic because of their close proximity to a severely ill proband.

A greater proportion of white relatives than nonwhites were available for interview. This may have reflected geographic separation, as many nonwhites had parents who lived in other countries. However, in a small proportion the reluctance of nonwhites to be interviewed may reflect negative attitudes toward medical and psychiatric services [Littlewood and Lipsedge, 1981]. Unfortunately, we did not record the reasons for nonparticipation in the family study and so this question remains unanswered.

In accord with all previous comparisons of the family history and family study methods, we found that the family history method seriously underestimates the

TABLE IV. Determinants of Best FH Estimate Diagnoses—Age of Relative

SADS diagnosis	No psychopathology			Major depression			Psychosis		
Age of relative	<35	35–55	>55	<35	35–55	>55	<35	35–55	>55
Cell count	52	66	175	12	22	15	12	10	8
Best FH estimate (BE) diagnosis of depression	2	4	4	1	10	9	0	2	1
Sensitivity of BE diagnosis of depression (%)	—	—	—	8	46	60	—	—	—
Best FH estimate (BE) diagnosis of psychosis	0	0	1	0	1	1	8	4	6
Sensitivity of BE diagnosis of psychosis (%)	—	—	—	—	—	—	67	40	75

TABLE V. Determinants of Best FH Estimate Diagnoses—Ethnicity

SADS diagnosis	No psychopathology		Major depression		Psychosis	
Ethnicity	W	NW	W	NW	W	NW
Cell count	133	42	39	10	18	12
Best FH estimate (BE) diagnosis of depression	7	4	17	3	3	0
Sensitivity of BE diagnosis of depression (%)	—	—	44	30	—	—
Best FH estimate (BE) diagnosis of psychosis	1	0	2	0	8	10
Sensitivity of BE diagnosis of psychosis (%)	—	—	—	—	44	83

amount of illness in first-degree relatives. Our sensitivity estimates indicate that 60% of cases of major depression and 40% of cases of psychosis may be missed when using the FH-RDC with all other available sources of supplementary information. In accordance with others, we found the specificity of family study diagnoses to be good, with 94% of diagnoses of major depression and 99% of diagnoses of psychosis being confirmed by subsequent SADS-L interviews.

Other than the reference (SADS-L) diagnosis, the most significant predictor of a positive best FH estimate diagnosis was the number of hospital admissions experienced by the relative. In addition to the extra information available from case notes to the researchers, the number of admissions probably reflects the severity of symptoms and therefore the extent to which the illness is known to family members. Orvaschel et al. [1982] found other indicators of severity for depression (previous treatment and vegetative symptoms) that predicted accurate reporting. The greater sensitivity for psychotic illness than for depression probably reflects the increased incapacity, greater likelihood of hospitalisation, and ease of identification of psychotic symptoms. With these factors in mind, we were surprised by the low sensitivity of the family history method in identifying psychotic individuals.

In the psychotic group alone, we found more sensitive reporting by nonwhite than white relatives. This was not a consequence of more hospitalisations in the subjects but may reflect other indications of severity of illness, e.g., more florid affect laden symptomatology has been reported in certain ethnic groups [Stevens, 1987]. Alternatively the differences may reflect different family structures with more accurate reporting by those relatives who live in close knit extended families and who therefore have more exposure to their relatives' symptoms [Lin et al., 1981]. Unfortunately, we have no data to test these explanations.

For the relatives with depression, informants were more likely to report symptoms for older than younger relative. Although this was not explained by their number of admissions, it may reflect more severe and chronic symptoms associated with depression in older age groups [Muller-Spahn et al., 1994].

Conclusions

The family history method is widely used in psychiatric research because it is relatively convenient, but in all samples studied to date, it has been shown to be of only moderate sensitivity. We have shown that relatives of psychotic probands are no more accurate in reporting psychopathology in first-degree relatives than relatives of patients with affective disorder. However, we cannot conclude that the family study method alone is adequate for gathering information about the relatives of a study population, as we found significant sampling bias that might distort prevalence rates of psychopathology in first-degree relatives if extrapolated to the whole population. Our recommendation is that in order to obtain accurate and unbiased information about psychopathology in the families of probands, it is not only important to interview directly as many relatives as possible, but also to obtain supplementary family history information for all identified relatives.

Our study has highlighted several possible sources of bias in the family study method, the awareness of which may help to minimise them in future studies. The implications of these potential sources of bias for statistical analysis depend on the purposes of the analysis. Effort must be made to adjust for bias when the aim is to obtain accurate estimates of the absolute morbid risk of a disorder, but this may be less important if the aim is to assess the relative risk associated with some "exposure" variable independent of the bias.

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